Remarks

This paper is further filed in response to the Office Action mailed October 29, 2007. Claims 1-104 are pending. By this amendment, claims 1, 3, 5, 7—9, 11, 13—17, 19, 29, 31, 35, 37, 39, 41, 43—45, 47, 49—53, 55—58, 60, 62, 67—69, 71, 73, 77—78, 80—81, 83, 85, 89—90, 92, 94, 96 and 100 are amended. The items raised in the October 29, 2007 Office Action are addressed in the remarks below.

I. Oath / Declaration

The Examiner objected to the oath/declaration for not identifying the mailing address of each inventor. A supplemental Oath/Declaration will be filed and will correct the error of the missing mailing address of one of the inventors.

II. Claim Objections

The Examiner objected to claim 3 because of the following informalities: claim 3 recites "at a site at least proximal to said interstitial space". Claim 3 has been amended to remove this informality.

III. Claim Rejections – 35 U.S.C. § 112

Claims 1—104 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The examiner asserts that there is no support for either the agent producing a disruption in the vessel is found in the specification and notes in the "Response to Argument" at page 4, that "the passageways are created by mechanical stress resulting of the flowable formulation." Amendments to the claims have amended the limitations where it is recited that "the agent or a fluid delivery vehicle

produces a disruption" to "a flowable formulation of the agent ..." Accordingly, Applicants respectfully request withdrawal of the rejection of those claims under section 112.

IV. Claim Rejections – 35 U.S.C. § 102

Claims 1-3, 7-11, 13-19, 21-23, 29-39, 43-47, and 49-100 were rejected under 35 U.S.C. § 102(e) as being anticipated by Wolff et al. (USP 6,867,196). Applicants respectfully request reconsideration of this rejection.

In the Exmainer's "Response to Arguments" at page 10, the Examiner asserts that

> In the broadest interpretation, permeability creates disruptions in the wall that are not normally there. The claims are not limited to "disruptive channels" but to disruptions in the vessels and these are encompassed by the teachings of Wolffe et al. Nor is tissue damage a prerequisite for disruption of the vessels. Rather, the condition of enhanced permeability and condition of enhanced larger pores is not a normal state of the vessel, the presence of these large pores signifies a disruption in their normal condition.

Independent claims 1, 8, 15, 37, 44, 51, 56, 67, 78, and 90 have been amended to clarify that a disruption in a vessel is where wall integrity is compromised creating a disruptive passageway in the wall of the vessel. Support for this amendment can be found at At column 5, lines 32—41:

> In another preferred embodiment of the subject methods, the flowable formulation of the active agent is introduced into the vascular deposition space in a manner such that the mechanical stress is of sufficient magnitude to provide for actual disruption of the vessel wall. **By disruption of the vessel wall is meant that the integrity of the wall is compromised such that actual passageways appear** between the interior of the vessel and regions beyond the inner wall surface, i.e. between the vascular deposition site and the target interstitial space.

Wolff, however, only describes enhanced delivery through natural channels (and not unnatural channels, i.e. disruptive channels, that are created due to wall integrity being compromised as provided in amended claims). In Wolff, at column 5, lines 31-38, the specification describes "large pores" existing in blood vessel walls and the use of pressure to enhance the delivery of DNA transfer through these large pores.

> This implies that plasmid DNA is capable of crossing microvascular walls by stringing through the large pores. Pressure may be one method for transfection of liver and skeletal muscle and may enhance plasmid DNA transfer by opening the endothelial barrier. Raising the intravascular hydrostatic pressure transiently increases water flow through the large pores and thereby forces the extravasation of plasmid DNA.

Thus, the delivery of DNA to a tissue bed is through existing blood vessel pores and not through disruption of the integrity of the vessel walls as claimed. The specification further describes delivery of DNA through vessel pores and the enhancement of such pores:

> We suggest that the rate of plasmid DNA extravasation can be increased by enhancing fluid convection through the large pores by raising the transmural pressure difference in selective regions. (Column 5, lines 49-53).
>
> For instance, VEGF in high doses significantly enhances fluid leakage, probably by enlarging pore size. (Column 5, lines 59-61).
>
> The hypothesis is that high intravascular a predetermined volume in a predetermined period of time is required to initiate flow through the pores. (Column 6, lines 40-42).

Wolf also describes increasing pressure for delivery through the microcapillary bed, also a pre-existing, i.e. natural channel of delivery from blood vessel to tissue. See, e.g., column 6, lines 25-26: "It may very well be that the microcapillary bed allows efficient delivery." Moreover, Wolff does not wish to cause tissue damage. See, e.g., column 7, lines 2-8:

> By creating a feedback between the intravenous pressure at the site of injection and the injection pump, a system can be created that automatically senses the target bed size and inject the proper amount of transfection solution. By limiting the injection volume per time unit, minimal tissue damage is incurred.

The amended claims, however, claim disruption of a vessel wall where the wall integrity is compromised, i.e., the is damaged.

Further, in col 9 lines 30-45, Wolff describes an "intravascular" route of administration as "within tubular structures...connected to a tissue or organ" and "within the cavity of the tubular structures, a bodily fluid flows to or from the body part." All these fluid channels are pre-existing and natural channels. The permeability of these channels can be modified, as Wolff described in column 11 by hydrostatic pressure, osmotic pressure, chemically, or biological agent, but these permeability changes simply increase the delivery of agents through natural channels in the vessel wall. Blood vessels are already somewhat permeable, Wolff simply describes enhancing this.

Accordingly, because the Wolff et al. patent fails to disclose every element of the claims at issue, those claims are patentable over and above the Wolff et al. patent. Applicants respectfully request withdrawal of the rejection of those claims under section 102(e).

IV. Claim Rejections – 35 U.S.C. § 103

The Examiner rejected claims 1, 4-6, 8, 12, 15, 20, 24, 28, 37, 40-42, 44, 48, 51, 56-59, 61-82, 84-93 and 95-104 under 35 U.S.C. § 103(a) as being unpatentable for obviousness over the Wolff et al. patent in vie of Makower et al (US 2002/0179098). As noted above, Wolff et al. explicitly teach not to damage the vessel or other tissue, as would

occur if the vessels are disrupted. In addition, as noted above, the Wolff et al. patent fails to disclose, teach, or suggest methods that include disruption of the vessel, or the administration of energy to the vessel. Because these limitations are not met by the art relied upon by the Examiner, there has been no prima facie showing of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection of these claims under section 103(a).

CONCLUSION

In view of the foregoing, it is submitted that the claims presented in this reissue application define patentable subject matter to which Applicant is entitled. Accordingly, consideration and allowance of the reissue application is requested.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 15-0665.

Respectfully submitted,

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